REMARKS

The amendments to the specification and abstract, replacing the term "dependent" with "activated" are made for the sake of clarity. As can be seen in the paragraph entitled "Technical Field," in some places the words "dependent" and "activated" are used interchangeably.

The additional amendments are made to correct obvious errors or to correct mistakes made in the translation of the Japanese language PCT application.

If the Office desires a complete new translation, please advise the undersigned accordingly.

The claims have been amended to correct grammatical errors, to remove unnecessary parentheses, and to narrow the scope of certain claims.

New claim 20 recites the portion of subject matter that was deleted from claim 14.

New claims 21-29 are method claims, reciting the use of the compounds set forth in the claims as filed, in the treatment of disease.

Accordingly, no new matter has been added. Entry and consideration of this Amendment is respectfully requested.

Respectfully submitted,

Kenneth J. Burchfiel
Registration No. 31,333

SUGHRUE, MION, ZINN,
MACPEAK & SEAS, PLLC
2100 Pennsylvania Avenue, N.W.
Washington, D.C. 20037-3213
Telephone: (202) 293-7060
Facsimile: (202) 293-7860

Date: February 2, 2001

APPENDIX

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The specification is changed as follows:

Page 1, paragraph encompassing lines 4-9:

This invention relates to a medicament, particularly a pyrazole derivative having an action to inhibit calcium release-activated [dependent] calcium channel, and a pharmaceutical composition containing the same as an active ingredient, particularly a calcium release-activated calcium channel inhibitor.

Page 4, paragraph encompassing lines 10-16:

WO 95/18097 discloses an anthranilic acid derivative represented by the following formula, which inhibits a cyclic GMP phosphodiesterase. In the formula [(I)], R_1 to R_4 represent H, a halogen atom, ..., pyrazolyl which may be substituted, ...; n is 0 to 6, W represents N or CH, Y represents O or S, ... (see said published patent application for details).

Page 4, partial paragraph encompassing lines 17-20:

An unexamined published Japanese patent application 9-59236 discloses an R^1, R^2-di-substituted benzamide derivative represented by the following formula [(1)], which is useful for the prevention and treatment of rheumatic,

Page 8, paragraph encompassing lines 19-29:

The invention also relates to a pharmaceutical composition, particularly a pharmaceutical composition for use in the inhibition of calcium release activated [-dependent] calcium channel,

which comprises a pyrazole derivative represented by the following general formula (I') or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier. Preferably, it relates to an IL-2 production inhibitor, a preventive or therapeutic agent for allergic, inflammatory or autoimmune diseases and a preventive or therapeutic agent for bronchial asthma or rheumatoid arthritis.

Page 20, partial paragraph encompassing lines 1-11:

carboxylic acid or a reactive derivative thereof, and examples of the reactive derivative include acid halides such as acid chlorides, acid bromides and the like; acid azides; active esters which can be prepared using methanol, ethanol, benzyl alcohol, phenol which may be substituted, 1-hydroxybenzotriazole, N-hydroxysuccinimide and the like; symmetric acid anhydrides; and mixed acid anhydrides with [ethoxycarbonyl chloride, isobutylcarbonyl chloride,] alkylcarboxylic acid, p-toluenesulfonic acid and the like. These reactive derivatives are commercially available or can be produced by the usual procedures.

Page 28, paragraph encompassing lines 3-8:

In particular, the compound of the present invention which is possessed of CRACC selective inhibitory activity over VOCC is useful, because it can cause CRACC inhibition without VOCC <u>inhibition</u>- [activation] induced undesirable reactions in central nervous system and cardiovascular system and the like.

Page 32, paragraph encompassing lines 6-13:

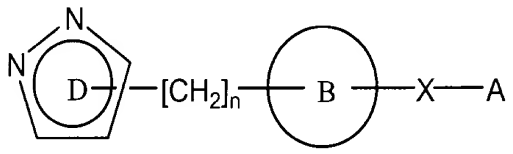
In four-week-old male BN rats <u>(Charles River, Japan)</u>, inhibitory effect on antigen-induced airway eosinophilia was tested in almost the same manner as the method reported by W.

Elwood *et al.* in *Inflamm. Res.*, 44: 83-86 (1995). In this connection, the drug was administered 30 minutes before the antigen exposure in the case of intravenous injection or 1 hour before and 3 hours after the antigen exposure in the case of oral administration.

IN THE CLAIMS:

The claims are amended as follows:

1. A pyrazole derivative represented by the following general formula (I) or a pharmaceutically acceptable salt thereof



(I)

wherein [(in the formula,] each symbol has the following meaning, [;]

D: pyrazolyl which may have 1 to 3 substituents selected from the group consisting of –Alk, –lower alkenyl, –lower alkynyl, –halogeno–lower alkyl, –Alk–cycloalkyl, –Alk–O–Alk, –cycloalkyl, –O–Alk, –COOH, –COO–Alk and –Hal,

n: 0 or 1,

B: phenylene, a nitrogen-containing, divalent, saturated ring group, or a monocyclic, divalent heteroaromatic ring group which may be substituted with Alk,

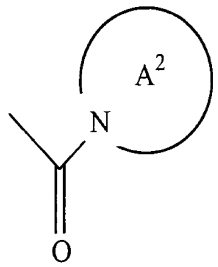
X: $-NR^1-CR^2R^3-$, $-CR^2R^3-NR^1-$, $-NR^1-SO_2-$, $-SO_2-NR^1-$ or $-CR^4=CR^5-$,

R^1: –H, –OH, –Alk, –O–Alk or –CO–Alk,

R^2 and R^3: the same or different from each other and each represents –H or –Alk, or R^2 and R^3 together form =O or =S,

R^4 and R^5: the same or different from each other and each represents –H, –Hal, –halogeno–lower alkyl or –Alk, and

A: benzene ring which may have one or more substituents; mono–, di– or tri–cyclic fused heteroaryl which may have one or more substituents; cycloalkyl which may have one or more substituents; a nitrogen-containing, saturated ring group which may have one or more substituents; lower alkenyl which may have one or more substituents; lower alkynyl which may have one or more substituents; or Alk which may have one or more substituents, or A and X may together form a group represented by a formula



[(]wherein A^2 is a nitrogen-containing hetero ring selected from the group consisting of 1–pyrrolidinyl, pyrazolidinyl, piperidino, piperazinyl, morpholino, 3,4–dihydro–2H–1,4–benzoxazin–4–yl and indolinyl, wherein said hetero ring may have one or more substituents[)], with the proviso that

(1) when D is 3,5–bis(trifluoromethyl) –1H–pyrazol–1–yl, n is 0, B is 1,4–phenylene and X is NHCO, A is a group other than 4–methyl–1,2,3–thiadiazol–5–yl,

(2) when D is 1–methyl–5–trifluoromethyl–1H–pyrazol–3–yl, n is 0, B is thiophene–2,5–diyl and X is CONH, A is a group other than 4-chlorophenyl,

(3) when D is l–methyl–3–trifluoromethyl–1H–pyrazol–5–yl, n is 0, B is thiophene–2,5–diyl and X is CONH, A is a group other than benzyl,

(4) when D is 4–ethoxycarbonyl–5–trifluoromethyl–1H–pyrazol–1–yl, n is 0, B is 1,4–phenylene and Y is NHCO, A is a group other than trichlorovinyl,

(5) when D is 1H–pyrazol–l–yl, n is 0, B is 1,4–phenylene and Y is NHCO, A is a group other than 2-ethoxyvinyl, and

(6) when n is 1, D is 1H–pyrazol–5–yl substituted with at least one trifluoromethyl group or 1H–pyrazol–l–yl substituted with at least one trifluoromethyl group[)].

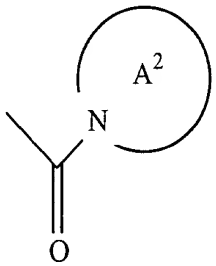
2. The pyrazole derivative or pharmaceutically acceptable salt thereof according to claim 1, wherein A is phenyl which may have one or more substituents of F group; mono–, di– or tri–cyclic fused heteroaryl which may have one or more substituents of F group; cycloalkyl which may have one or more substituents of F group; a nitrogen–containing, saturated ring group which may have one or more substituents of F group; lower alkenyl which may have one or more substituents of G group; lower alkynyl which may have one or more substituents of G group; or Alk which may have one or more substituents of G group,

wherein the F group is a group consisting of –Alk, –lower alkenyl, –lower alkynyl, –Hal, $-NH_2$, –NH(Alk), $-N(Alk)_2$, $-NO_2$, –CN, –OH, –O–Alk, –O–CO–Alk, –SH, –S–Alk, –COOH, –COO–Alk, –CO–Alk, –CHO, $-CONH_2$, –CONH(Alk), $-CON(Alk)_2$, –SO–Alk, SO_2Alk,

$-SO_2NH_2$, $-SO_2NH-(Alk)$, $-SO_2N(Alk)_2$, –aryl, –cycloalkyl, –O–Alk–O–, –halogeno–lower alkyl, $-Alk-NH_2$, –Alk–NH(Alk), $-Alk-N(Alk)_2$, –Alk–OH, –Alk–O–Alk, –Alk–SH, –Alk–S–Alk, –Alk–COOH, –Alk–COO–Alk, –Alk–CO–Alk, –Alk–CHO, $-Alk-CONH_2$, –Alk–CONH(Alk), $-Alk-CON(Alk)_2$, –Alk–SO–Alk, $-Alk-SO_2-Alk$, $-Alk-SO_2NH_2$, $-Alk-SO_2NH(Alk)$, $-Alk-SO_2N(Alk)_2$, –Alk–aryl and –Alk–cycloalkyl,

and the G group is a group consisting of –Hal, $-NH_2$, –NH(Alk), $-N(Alk)_2$, $-NO_2$, –CN, –OH, –O–Alk, –O–CO–Alk, –SH, –S–Alk, –COOH, –COO–Alk, –CO–Alk, –CHO, $-CONH_2$, –CONH(Alk), $-CON(Alk)_2$, –SO–Alk, $-SO_2-Alk$, $-SO_2NH_2$, $-SO_2NH-(Alk)$, $-SO_2N(Alk)_2$, aryl which may have one or more substituents of F group; mono–, di– or tri–cyclic fused heteroaryl which may have one or more substituents of F group; cycloalkyl which may have one or more substituents of F group and a nitrogen–containing, saturated ring group which may have one or more substituents of F group,

or A and X may together form a group represented by a formula



[()]wherein A^2 is a nitrogen–containing hetero ring selected from the group consisting of 1–pyrrolidinyl, pyrazolidinyl, piperidino, 1–piperazinyl, morpholino, 3,4–dihydro–2H–1,4–

benzoxazin–4–yl and indolinyl, wherein said hetero ring may have one or more substituents of F group[)].

3. The pyrazole derivative or pharmaceutically acceptable salt thereof according to claim 2, wherein

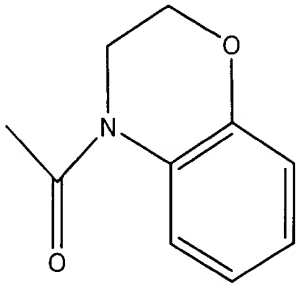
B is phenylene; piperidine–1,4–diyl; or a monocyclic, divalent heteroaromatic ring group selected from the class consisting of thiophene, furan, pyrrole, imidazole, pyrazole, thiazole, isothiazole, oxazole, isoxazole, thiadiazole, pyridine, pyrazine, pyridazine and pyrimidine, which may be substituted with Alk,

X is –NH–CO–, –NH–CH_2–, –N(OH)–CO–, –N(Alk)–CO–, –CO–NH–, –CH_2–NH–, –CO–N(OH)–, –CO–N(Alk)–, –SO_2NH–, –$NHSO_2$– or –CH=C(Hal) –,

A is aryl which may have one or more substituents of group F; mono–, di– or tri–cyclic fused heteroaryl selected from the group consisting of thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, tetrazolyl, triazolyl, thiadiazolyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, indolyl, isoindolyl, isoquinolyl, quinolyl, quinoxanyl, phthalazinyl, imidazopyridyl, quinazolinyl and cinnolinyl, which may have one or more substituents of group F; cycloalkyl; a nitrogen–containing, saturated ring selected from the group consisting of pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidyl, piperazinyl and morpholinyl, which may be substituted with one or more Alk; lower alkynyl which may be substituted with one or more Hal; lower alkenyl which may be substituted with one or more Hal; or Alk which may be substituted with one or more Hal, and the F group is a group consisting of –Alk, –lower alkenyl, –lower alkynyl, –Hal, –NH_2, –NH(Alk), –$N(Alk)_2$, –NO_2, –CN, –OH, –O–Alk,

–O–CO–Alk, –SH, –S–Alk, –COOH, –COO–Alk, –CO–Alk, –CHO, $–CONH_2$, –CONH(Alk), $–CON(Alk)_2–$, –SO–Alk, $–SO_2–Alk$, $–SO_2NH_2$, $–SO_2NH–(Alk)$ and $–SO_2N(Alk)_2$,

or A and X may together form a group represented by a formula



4. The pyrazole derivative or pharmaceutically acceptable salt thereof according to claim 3, wherein

n is 0, D is pyrazolyl which may have 1 to 3 substituents selected from –Alk, –halogeno–lower alkyl, –COOH and –COO–Alk,

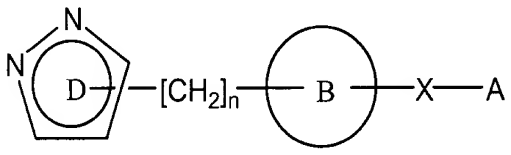
B is phenylene or a monocyclic, divalent heteroaromatic ring group selected from the class consisting of thiophene, furan, thiazole, pyridine and pyrimidine, which may be substituted with Alk,

X is –NH–CO–, –N(OH)–CO–, –CO–NH–, $–CH_2–NH–$ or –CO–N(Alk) –, and

A is phenyl which may have one or more substituents selected from the group consisting of –Alk, –Hal, $–NH_2$, $–N(Alk)_2$, $–NO_2$, –CN, –OH, –O–Alk and –COO–Alk; mono–, di– or tri–cyclic fused heteroaryl selected from the group consisting of thienyl, pyrrolyl, imidazolyl,

thiazolyl, oxazolyl, tetrazolyl, triazolyl, thiadiazolyl, pyridyl, pyrazinyl and isoquinolyl, which may be substituted with Alk; cycloalkyl; lower alkenyl which may be substituted with one or more Hal; or Alk.

10. A pharmaceutical composition which comprises a pyrazole derivative represented by the following general formula (I') or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier



(I')

wherein [(in the formula,] each symbol has the following meaning, [;]

D: pyrazolyl which may have 1 to 3 substituents selected from the group consisting of –Alk, –lower alkenyl, –lower alkynyl, –halogeno–lower alkyl, –Alk–cycloalkyl, –Alk–O–Alk, –cycloalkyl, –O–Alk, –COOH, –COO–Alk and –Hal,

n: 0 or 1,

B: phenylene, a nitrogen–containing, divalent, saturated ring group, or a monocyclic, divalent heteroaromatic ring group which may be substituted with Alk,

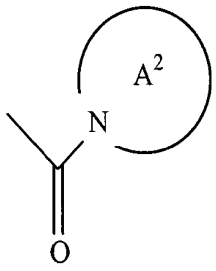
X: $-NR^1-CR^2R^3-$, $-CR^2R^3-NR^1-$, $-NR^1-SO_2-$, $-SO_2-NR^1-$ or $-CR^4=CR^5-$,

R^1: –H, –OH, –Alk, –O–Alk or –CO–Alk,

R^2 and R^3: the same or different from each other and each represents –H or –Alk, or R^2 and R^3 together form =O or =S,

R^4 and R^5: the same or different from each other and each represents –H, –Hal, –halogeno–lower alkyl or –Alk, and

A: benzene ring which may have one or more substituents; mono–, di– or tri–cyclic fused heteroaryl which may have one or more substituents; cycloalkyl which may have one or more substituents; a nitrogen–containing, saturated ring group which may have one or more substituents; lower alkenyl which may have one or more substituents; lower alkynyl which may have one or more substituents; or Alk which may have one or more substituents, or A and X may together form a group represented by a formula



[(]wherein A^2 is a nitrogen–containing hetero ring selected from the group consisting of l–pyrrolidinyl, pyrazolidinyl, piperidino, piperazinyl, morpholino, 3,4–dihydro–2H–1,4–benzoxazin–4–yl and indolinyl, wherein said hetero ring may have one or more substituents[)], with the proviso that

(1) when n is 1, D is 1H–pyrazol–5–yl substituted with at least one trifluoromethyl group or 1H–pyrazol–l–yl substituted with at least [leaest] one trifluoromethyl group, and

(2) when D is 3,5–bis(trifluoromethyl) –1H–pyrazo1–1–yl, n is 0, B is l,4–phenylene and X is NHCO, A is a group other than 4–methyl–l,2,3–thiadiazol–5–yl [)].

11. The pharmaceutical composition according to claim 10, which is a calcium release-activated [dependent] calcium channel inhibitor.

13. The pharmaceutical composition according to claim 12, which is a preventive or therapeutic agent for an allergic, inflammatory or autoimmune disease [diseases].

14. The pharmaceutical composition according to claim 13, which is a preventive or therapeutic agent for bronchial asthma [or rheumatoid arthritis].

15. The pharmaceutical composition according to any one of claims 10 to 14, or 20, wherein D is pyrazolyl substituted with at least one trifluoromethyl group.

16. The pharmaceutical composition according to any one of claims 10 to 14, or 20, wherein D is 1H–pyrazol–5–yl substituted with at least one trifluoromethyl group or 1H–pyrazol–1–yl substituted with at least one trifluoromethyl group.

17. The pharmaceutical composition according to any one of claims 10 to 14, or 20, wherein X is –NH–CO– or –CO–NH–.

18. The pharmaceutical composition according to any one of claims 10 to 14, or 20, wherein D is 1–methyl–3–trifluoromethyl–1H–pyrazol–5–yl and A is phenyl which may be substituted with Hal.

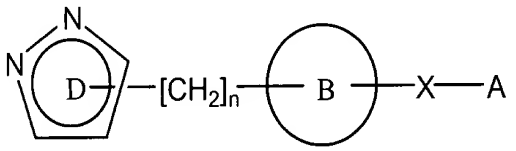
19. The pharmaceutical composition according to any one of claims 10 to 14, or 20, wherein D is 3,5–bis(trifluoromethyl)–1H–pyrazol–1–yl and A is monocyclic heteroaryl selected from the group consisting of thiazolyl, thiadiazolyl, thienyl and pyridyl, which may be substituted with Alk.

Claims 20-29 are added as new claims.

IN THE ABSTRACT OF DISCLOSURE:

The abstract is changed as follows:

The present invention is directed to drugs, in particular, pyrazole derivatives represented by the following general formula (I)



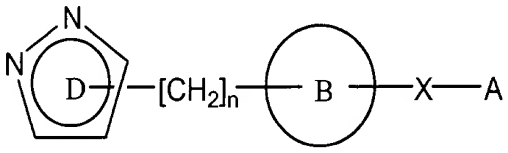
(I)

which have a calcium release-activated calcium channel inhibitory effect and medicinal compositions, in particular, calcium release-activated calcium channel inhibitors containing the above compounds as the active ingredient, wherein each substituent is defined in the specification.

The present invention also relates to a pharmaceutical composition containing an effective amount of the compound of formula (I) and a pharmaceutically effective carrier.

The present invention further relates to methods of treatment of diseases associated with calcium release-activated calcium channels, diseases associated with IL-2 production, and methods of treatment of allergic, inflammatory or auto-immune diseases.

[Drugs, in particular, pyrazole derivatives represented by the following general formula (I) which have a calcium release- dependent calcium channel inhibitory effect and medicinal compositions, in particular, calcium release- dependent calcium channel inhibitors containing the above compounds as the active ingredient,



(I)

(in the formula, each symbol has the following meaning:

B: phenylene, a nitrogen-containing, divalent, saturated ring group, or a monocyclic, divalent heteroaromatic ring group which may be substituted with Alk,

X: $-NR^1-CR^2R^3-$, $-CR^2R^3-NR^1-$, $-NR^1-SO_2-$, $-SO_2-NR^1-$ or $-CR^4=CR^5-$,

A: benzene ring which may have one or more substituents; mono–, di– or tricyclic fused heteroaryl which may have one or more substituents; cycloalkyl which may have one or more substituents; a nitrogen-containing, saturated ring group which may have one or more substituents; lower alkenyl which may have one or more substituents; lower alkynyl which may have one or more substituents; or Alk which may have one or more substituents).]